FILE 'HOME' ENTERED AT 09:09:14 ON 20 JUN 2006

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=> file .nash
=> s undecaprenyl pyrophosphate synthase and crystal
L1            5 FILE MEDLINE
L2            9 FILE CAPLUS
L3            7 FILE SCISEARCH
L4            3 FILE LIFESCI
L5            7 FILE BIOSIS
L6            5 FILE EMBASE

TOTAL FOR ALL FILES
L7           36 UNDECAPRENYL PYROPHOSPHATE SYNTHASE AND CRYSTAL

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8           13 DUP REM L7 (23 DUPLICATES REMOVED)

=> d 1-13 ibib abs

L8   ANSWER 1 OF 13  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2006:251444  SCISEARCH Full-text
THE GENUINE ARTICLE: 017HY
TITLE:               Manipulation of prenyl chain length determination
                     mechanism of cis-prenyltransferases
AUTHOR:              Kharel Y; Takahashi S; Yamashita S; Koyama T (Reprint)
CORPORATE SOURCE:    Tohoku Univ, Inst Multidisciplinary Res Adv Mat, Aoba Ku,
                     Katahira 2-1-1, Sendai, Miyagi, Japan (Reprint); Tohoku
                     Univ, Inst Multidisciplinary Res Adv Mat, Aoba Ku, Sendai,
                     Miyagi, Japan
                     koyama@tagen.tohoku.ac.jp
COUNTRY OF AUTHOR:   Japan
SOURCE:              FEBS JOURNAL, (FEB 2006) Vol. 273, No. 3, pp. 647-657.
                     ISSN: 1742-464X.
PUBLISHER:           BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ,
                     OXON, ENGLAND.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     34
ENTRY DATE:          Entered STN: 16 Mar 2006
                     Last Updated on STN: 16 Mar 2006
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB          The carbon backbones of Z,E-mixed isoprenoids are synthesized by sequential cis-
            condensation of isopentenyl diphosphate (IPP) and an allylic diphosphate through
            actions of a series of enzymes called cis-prenyl transferases. Recent molecular
            analyses of Micrococcus luteus B-P 26 undecaprenyl diphosphate (UPP, C-55) synthase
            [Fujihashi M, Zhang Y-W, Higuchi Y, Li X-Y, Koyama T & Miki K (2001) Proc Natl Acad
            Sci USA 98, 4337-4342.] showed that not only the primary structure but also the
            crystal structure of cis-prenyltransferases were totally different from those of
            trans-prenyltransferases. Although many studies on structure-function
            relationships of cis-prenyltransferases have been reported, regulation mechanisms
            for the ultimate prenyl chain length have not yet been elucidated. We report here
            that the ultimate chain length of prenyl products can be controlled through
            Structural manipulation of UPP synthase of M. luteus B-P 26, based on comparisons
            between structures of various cis-prenyltransferases. Replacements of Ala72,
            Phe73, and Trp78, which are located in the proximity Of the Substrate binding site,
            with Leu - as in Z,E-farnesyl diphosphate (C-15) synthase - resulted in shorter
            ultimate products with C20-35. Additional mutation of F223H resulted in even
            shorter products. On the other hand, insertion of charged residues originating
            from long-chain cis-prenyltransferases into helix-3, which participates in
            constitution of the large hydrophobic cleft, resulted in lengthening of the
            ultimate product chain length, leading to C60-75. These results helped us
            understand reaction mechanisms of cis-prenyltransferase including regulation of the
            ultimate prenyl chain length.

L8   ANSWER 2 OF 13     MEDLINE on STN                DUPLICATE 1
ACCESSION NUMBER:    2005266340     MEDLINE Full-text
DOCUMENT NUMBER:     PubMed ID: 15788389
```

TITLE: Crystal structures of undecaprenyl pyrophosphate synthase in complex with magnesium, isopentenyl pyrophosphate, and farnesyl thiopyrophosphate: roles of the metal ion and conserved residues in catalysis.
AUTHOR: Guo Rey-Ting; Ko Tzu-Ping; Chen Annie P-C; Kuo Chih-Jung; Wang Andrew H-J; Liang Po-Huang
CORPORATE SOURCE: Taiwan International Graduate Program, Academia Sinica, Taipei 115, Taiwan.
SOURCE: The Journal of biological chemistry, (2005 May 27) Vol. 280, No. 21, pp. 20762-74. Electronic Publication: 2005-03-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1X06; PDB-1X07; PDB-1X08; PDB-1X09
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 24 May 2005
Last Updated on STN: 16 Aug 2005
Entered Medline: 15 Aug 2005

AB Undecaprenyl pyrophosphate synthase (UPPs) catalyzes the consecutive condensation reactions of a farnesyl pyrophosphate (FPP) with eight isopentenyl pyrophosphates (IPP), in which new cis-double bonds are formed, to generate undecaprenyl pyrophosphate that serves as a lipid carrier for peptidoglycan synthesis of bacterial cell wall. The structures of Escherichia coli UPPs were determined previously in an orthorhombic crystal form as an apoenzyme, in complex with Mg(2+)/sulfate/Triton, and with bound FPP. In a further search of its catalytic mechanism, the wild-type UPPs and the D26A mutant are crystallized in a new trigonal unit cell with Mg(2+)/IPP/farnesyl thiopyrophosphate (an FPP analogue) bound to the active site. In the wild-type enzyme, Mg(2+) is coordinated by the pyrophosphate of farnesyl thiopyrophosphate, the carboxylate of Asp(26), and three water molecules. In the mutant enzyme, it is bound to the pyrophosphate of IPP. The [Mg(2+)] dependence of the catalytic rate by UPPs shows that the activity is maximal at [Mg(2+)] = 1 mm but drops significantly when Mg(2+) ions are in excess (50 mm). Without Mg(2+), IPP binds to UPPs only at high concentration. Mutation of Asp(26) to other charged amino acids results in significant decrease of the UPPs activity. The role of Asp(26) is probably to assist the migration of Mg(2+) from IPP to FPP and thus initiate the condensation reaction by ionization of the pyrophosphate group from FPP. Other conserved residues, including His(43), Ser(71), Asn(74), and Arg(77), may serve as general acid/base and pyrophosphate carrier. Our results here improve the understanding of the UPPs enzyme reaction significantly.

L8 ANSWER 3 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:12342 SCISEARCH Full-text
THE GENUINE ARTICLE: 961JU
TITLE: Crystal structures and catalytic mechanism of undecaprenyl pyrophosphate synthase
AUTHOR: ANON
SOURCE: EUROPEAN BIOPHYSICS JOURNAL WITH BIOPHYSICS LETTERS, (AUG 2005) Vol. 34, No. 6, pp. 662-662.
ISSN: 0175-7571.
PUBLISHER: SPRINGER, 233 SPRING STREET, NEW YORK, NY 10013 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

L8 ANSWER 4 OF 13 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:63959 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600064319
TITLE: Crystal structures and catalytic mechanism of undecaprenyl pyrophosphate synthase.
AUTHOR(S): Ko, T.-P. [Reprint Author]; Guo, R.-T.; Chen, A. P.-C.; Kuo, C.-J.; Wang, A. H.-J.; Liang, P.-H.
SOURCE: European Biophysics Journal, (AUG 2005) Vol. 34, No. 6, pp.

662.
Meeting Info.: Joint 15th IUPAB and 5th EBSA International Biophysics Congress. Montpellier, FRANCE. August 27 -September 01, 2005. Int Union Pure & Appl Biophys; European Biophys Soc Assoc.
CODEN: EBJOE8. ISSN: 0175-7571.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jan 2006
Last Updated on STN: 11 Jan 2006

L8 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005063034 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15447632
TITLE: Substrate and product specificities of cis-type **undecaprenyl pyrophosphate synthase.**
AUTHOR: Chen Annie P-C; Chang Sing-Yang; Lin Yu-Chung; Sun Yang-Sheng; Chen Chao-Tsen; Wang Andrew H-J; Liang Po-Huang
CORPORATE SOURCE: Institute of Biochemical Sciences, National Taiwan University, Taipei 106, Taiwan, Republic of China.
SOURCE: The Biochemical journal, (2005 Feb 15) Vol. 386, No. Pt 1, pp. 169-76.
Journal code: 2984726R. E-ISSN: 1470-8728.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 5 Feb 2005
Last Updated on STN: 3 Aug 2005
Entered Medline: 2 Aug 2005

AB UPPS (**undecaprenyl pyrophosphate synthase**) catalyses consecutive condensation reactions of FPP (farnesyl pyrophosphate) with eight isopentenyl pyrophosphates to generate C55 UPP, which serves as a lipid carrier for bacterial peptidoglycan biosynthesis. We reported the co-crystal structure of Escherichia coli UPPS in complex with FPP. Its phosphate head-group is bound to positively charged arginine residues and the hydrocarbon moiety interacts with hydrophobic amino acids including L85, L88 and F89, located on the alpha3 helix of UPPS. We now show that the monophosphate analogue of FPP binds UPPS with an eight times lower affinity (K(d)=4.4 microM) compared with the pyrophosphate analogue, a result of a larger dissociation rate constant (k(off)=192 s(-1)). Farnesol (1 mM) lacking the pyrophosphate does not inhibit the UPPS reaction. GGPP (geranylgeranyl pyrophosphate) containing a larger C20 hydrocarbon tail is an equally good substrate (K(m)=0.3 microM and kcat=2.1 s(-1)) compared with FPP. The shorter C10 GPP (geranyl pyrophosphate) displays a 90-fold larger K(m) value (36.0+/-0.1 microM) but similar kcat value (1.7+/-0.1 s(-1)) compared with FPP. Replacement of L85, L88 or F89 with Ala increases FPP and GGPP K(m) values by the same amount, indicating that these amino acids are important for substrate binding, but do not determine substrate specificity. With GGPP as a substrate, UPPS still catalyses eight isopentenyl pyrophosphate condensation reactions to synthesize C60 product. Computer modelling suggests that the upper portion of the active-site tunnel, where cis double bonds of the product reside, may be critical for determining the final product chain length.

L8 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:355073 CAPLUS Full-text
DOCUMENT NUMBER: 140:352650
TITLE: Crystal structure of Staphylococcus aureus **undecaprenyl pyrophosphate synthase** and its use in drug design
INVENTOR(S): Pandit, Jayvardhan; Ammirati, Mark
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| WO 2004035770 | | A1 | 20040429 | WO 2003-IB4529 | 20031010 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003269334 | | A1 | 20040504 | AU 2003-269334 | 20031010 |
| EP 1556483 | | A1 | 20050727 | EP 2003-751115 | 20031010 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| US 2005208639 | | A1 | 20050922 | US 2003-688167 | 20031017 |
| PRIORITY APPLN. INFO.: | | | | US 2002-419952P P | 20021021 |
| | | | | WO 2003-IB4529 W | 20031010 |

AB The invention relates to crystal structure of Staphylococcus aureus undecaprenyl pyrophosphate synthase and its use in drug design. The invention relates to the crystal structure of undecaprenyl pyrophosphate synthase from Staphylococcus aureus and the interaction with a cofactor and ligands. The invention also relates to the structure of ligand and cofactor binding sites.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:802264 CAPLUS Full-text
DOCUMENT NUMBER: 141:289002
TITLE: Crystal structures of Streptococcus pneumoniae undecaprenyl pyrophosphate synthetase and its use in screening for inhibitors
INVENTOR(S): Fennell, Kimberly F.; Mansour, Mahmoud N.; Qiu, Xiayang
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 83 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004191271 | A1 | 20040930 | US 2004-815402 | 20040331 |
| WO 2004087907 | A2 | 20041014 | WO 2004-IB903 | 20040318 |
| WO 2004087907 | A3 | 20041202 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1611234 | A2 | 20060104 | EP 2004-721605 | 20040318 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK | | | |
| PRIORITY APPLN. INFO.: | | | US 2003-459053P P | 20030331 |
| | | | WO 2004-IB903 W | 20040318 |

AB The invention provides crystal structures of Streptococcus pneumoniae undecaprenyl pyrophosphate synthetase and its use in screening for inhibitors. The invention also relates to the structure of ligand and cofactor binding sites of undecaprenyl pyrophosphate synthase.

L8 ANSWER 8 OF 13 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:174548 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400176323
TITLE: Crystal structure of octaprenyl pyrophosphate synthase from hyperthermophilic Thermotoga maritima and mechanism of product chain length determination.
AUTHOR(S): Guo, Rey-Ting; Kuo, Chih-Jung; Chou, Chia-Cheng; Ko, Tzu-Ping; Shr, Hui-Lin; Liang, Po-Huang [Reprint Author]; Wang, Andrew H.-J. [Reprint Author]
CORPORATE SOURCE: Inst. of Biological Chemistry, Academia Sinica, 128 Academia Rd., Taipei, 115, Taiwan phliang@gate.sinica.edu.tw; ahjwang@gate.sinica.edu.tw
SOURCE: Journal of Biological Chemistry, (February 6 2004) Vol. 279, No. 6, pp. 4903-4912. print. CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
OTHER SOURCE: Protein Data Bank-1V4E; Protein Data Bank-1V4H; Protein Data Bank-1V4I; Protein Data Bank-1V4J; Protein Data Bank-1V4K
ENTRY DATE: Entered STN: 31 Mar 2004
Last Updated on STN: 31 Mar 2004

AB Octaprenyl pyrophosphate synthase (OPPs) catalyzes consecutive condensation reactions of farnesyl pyrophosphate (FPP) with isopentenyl pyrophosphate (IPP) to generate C40 octaprenyl pyrophosphate (OPP), which constitutes the side chain of bacterial ubiquinone or menaquinone. In this study, the first structure of long chain C40-OPPs from Thermotoga maritima has been determined to 2.28-ANG resolution. OPPs is composed entirely of alpha-helices joined by connecting loops and is arranged with nine core helices around a large central cavity. An elongated hydrophobic tunnel between D and F alpha-helices contains two DDXXD motifs on the top for substrate binding and is occupied at the bottom with two large residues Phe-52 and Phe-132. The products of the mutant F132A OPPs are predominantly C50, longer than the C40 synthesized by the wild-type and F52A mutant OPPs, suggesting that Phe-132 is the key residue for determining the product chain length. Ala-76 and Ser-77 located close to the FPP binding site and Val-73 positioned further down the tunnel were individually mutated to larger amino acids. A76Y and S77F mainly produce C20 indicating that the mutated large residues in the vicinity of the FPP site limit the substrate chain elongation. Ala-76 is the fifth amino acid upstream from the first DDXXD motif on helix D of OPPs, and its corresponding amino acid in FPPs is Tyr. In contrast, V73Y mutation led to additional accumulation of C30 intermediate. The new structure of the trans-type OPPs, together with the recently determined cis-type UPPs, significantly extends our understanding on the biosynthesis of long chain polyprenyl molecules.

L8 ANSWER 9 OF 13 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004152208 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15044730
TITLE: Substrate binding mode and reaction mechanism of **undecaprenyl pyrophosphate synthase** deduced from crystallographic studies.
AUTHOR: Chang Sing-Yang; Ko Tzu-Ping; Chen Annie P-C; Wang Andrew H-J; Liang Po-Huang
CORPORATE SOURCE: Institute of Biological Chemistry, Academia Sinica, Taipei 115, Taiwan.
SOURCE: Protein science : a publication of the Protein Society, (2004 Apr) Vol. 13, No. 4, pp. 971-8. Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 27 Mar 2004
Last Updated on STN: 22 Oct 2004
Entered Medline: 21 Oct 2004

AB **Undecaprenyl pyrophosphate synthase** (UPPs) catalyzes eight consecutive condensation reactions of farnesyl pyrophosphate (FPP) with isopentenyl pyrophosphate (IPP) to form a 55-carbon long-chain product. We previously reported the crystal structure of the apo-enzyme from Escherichia coli and the structure of UPPs in complex with sulfate ions (resembling pyrophosphate of substrate), Mg(2+), and two Triton molecules (product-like). In the present study, FPP substrate was soaked into the UPPs crystals, and the complex structure was solved. Based on the crystal structure, the pyrophosphate head group of FPP is bound to the backbone NHs of Gly29 and Arg30 as well as the side chains of Asn28,

Arg30, and Arg39 through hydrogen bonds. His43 is close to the C2 carbon of FPP and may stabilize the farnesyl cation intermediate during catalysis. The hydrocarbon moiety of FPP is bound with hydrophobic amino acids including Leu85, Leu88, and Phe89, located on the alpha3 helix. The binding mode of FPP in cis-type UPPs is apparently different from that of trans-type and many other prenyltransferases which utilize Asprich motifs for substrate binding via Mg(2+). The new structure provides a plausible mechanism for the catalysis of UPPs.

L8 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:454585 CAPLUS Full-text
DOCUMENT NUMBER: 139:32518
TITLE: **Crystal structure of Streptococcus pneumoniae undecaprenyl pyrophosphate synthase and its use in structure-based drug design**
INVENTOR(S): Concha, Nestor O.; Janson, Cheryl A.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 516 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003048733 | A2 | 20030612 | WO 2002-US38715 | 20021202 |
| WO 2003048733 | A3 | 20050310 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002346643 | A1 | 20030617 | AU 2002-346643 | 20021202 |
| EP 1527167 | A2 | 20050504 | EP 2002-784715 | 20021202 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, SK | | | | |

PRIORITY APPLN. INFO.: US 2001-337227P P 20011205
WO 2002-US38715 W 20021202

AB The **crystal** structures of Streptococcus pneumoniae **undecaprenyl pyrophosphate synthase** (UPPS) in its native state and in complexes with the substrates farnesyl pyrophosphate and isopentenyl pyrophosphate are provided. The structures show that UPPS is a dimer with an extensive contact area along a dimer interface. A shallow cleft harbors numerous conserved residues and delimits an active site. Several of these residues are disordered in a native enzyme but become well ordered in substrate-bound complexes. The **crystal** structures of the complexes with each of two substrates provide a detailed description of these substrates' mode of binding, a structure of the Michaelis complex, and certain critical residues involved in binding of substrates. The three-dimensional structure of the UPPS active site allows structure-based design of inhibitors.

L8 ANSWER 11 OF 13 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003351054 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12756244
TITLE: Catalytic mechanism revealed by the **crystal** structure of **undecaprenyl pyrophosphate synthase** in complex with sulfate, magnesium, and triton.
AUTHOR: Chang Sing-Yang; Ko Tzu-Ping; Liang Po-Huang; Wang Andrew H-J
CORPORATE SOURCE: Institute of Biological Chemistry, Academia Sinica, Taipei 11529, Taiwan.
SOURCE: The Journal of biological chemistry, (2003 Aug 1) Vol. 278, No. 31, pp. 29298-307. Electronic Publication: 2003-05-19.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1UEH
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 29 Jul 2003
Last Updated on STN: 11 Sep 2003
Entered Medline: 10 Sep 2003

AB Undecaprenyl pyrophosphate synthase (UPPs) catalyzes chain elongation of farnesyl pyrophosphate (FPP) to undecaprenyl pyrophosphate (UPP) via condensation with eight isopentenyl pyrophosphates (IPP). UPPs from Escherichia coli is a dimer, and each subunit consists of 253 amino acid residues. The chain length of the product is modulated by a hydrophobic active site tunnel. In this paper, the crystal structure of E. coli UPPs was refined to 1.73 A resolution, which showed bound sulfate and magnesium ions as well as Triton X-100 molecules. The amino acid residues 72-82, which encompass an essential catalytic loop not seen in the previous apoenzyme structure (Ko, T.-P., Chen, Y. K., Robinson, H., Tsai, P. C., Gao, Y.-G., Chen, A. P.-C., Wang, A. H.-J., and Liang, P.-H. (2001) J. Biol. Chemical 276, 47474-47482), also became visible in one subunit. The sulfate ions suggest locations of the pyrophosphate groups of FPP and IPP in the active site. The Mg2+ is chelated by His-199 and Glu-213 from different subunits and possibly plays a structural rather than catalytic role. However, the metal ion is near the IPP-binding site, and double mutation of His-199 and Glu-213 to alanines showed a remarkable increase of Km value for IPP. Inside the tunnel, one Triton surrounds the top portion of the tunnel, and the other occupies the bottom part. These two Triton molecules may mimic the hydrocarbon moiety of the UPP product in the active site. Kinetic analysis indicated that a high concentration (>1%) of Triton inhibits the enzyme activity.

L8 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003581736 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14661956
TITLE: Identification of the active conformation and the importance of length of the flexible loop 72-83 in regulating the conformational change of undecaprenyl pyrophosphate synthase.
AUTHOR: Chang Sing-Yang; Chen Yi-Kai; Wang Andrew H-J; Liang Po-Huang
CORPORATE SOURCE: Institute of Biological Chemistry, Academia Sinica, Taipei 11529, Taiwan.
SOURCE: Biochemistry, (2003 Dec 16) Vol. 42, No. 49, pp. 14452-9.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 16 Dec 2003
Last Updated on STN: 9 Apr 2004
Entered Medline: 8 Apr 2004

AB Increasing evidence has shown that intrinsic disorder of proteins plays a key role in their biological functions. In the case of undecaprenyl pyrophosphate synthase (UPPs), which catalyzes the chain elongation of farnesyl pyrophosphate (FPP) to undecaprenyl pyrophosphate via eight consecutive condensation reactions with isopentenyl pyrophosphate, a highly flexible loop 72-83 was previously linked to protein conformational change required for catalysis [Chen, Y. H., Chen, A. P.-C., Chen, C. T., Wang, A. H.-J., and Liang, P. H., (2002) J. Biol. Chemical 277, 7369-7376]. The crystal structure and fluorescence studies suggested that the alpha3 helix connected to the loop moves toward the active site when the substrate is bound. To identify the active conformation and study the role of the loop for conformational change, the UPPs mutants with amino acids inserted into or deleted from the loop were examined. The inserted mutant with extra Ala residues fails to display the intrinsic fluorescence quenching upon FPP binding, and its crystal structure reveals only the open form. These phenomena appear to be different from the wild-type enzyme in which open and closed conformers were observed and suggest that the extended loop fails to pull the alpha3 helix and/or the extra amino acids in the loop cause steric hindrance on the alpha3 helix movement. The loop-shortening mutants with deletion of V82 and S83 or S72 also adopt an open conformation with the loop stretched, although they show decreased intrinsic fluorescence with FPP bound, similar to that seen in the wild-type enzyme. We conclude that the closed conformation is apparently the

active conformation. Change of the length of the loop 72-83 impairs the ability of conformational change and causes remarkably lower activity of UPPs.

L8 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2001:925549 CAPLUS Full-text

DOCUMENT NUMBER: 136:147088

TITLE: Mechanism of product chain length determination and the role of a flexible loop in Escherichia coli undecaprenyl-pyrophosphate synthase catalysis

AUTHOR(S): Ko, Tzu-Ping; Chen, Yi-Kai; Robinson, Howard; Tsai, Pei-Chun; Gao, Yi-Gui; Chen, Annie P.-C.; Wang, Andrew H.-J.; Liang, Po-Huang

CORPORATE SOURCE: Institute of Biological Chemistry, Academia Sinica, Taipei, 115, Taiwan

SOURCE: Journal of Biological Chemistry (2001), 276(50), 47474-47482
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Escherichia coli undecaprenyl-pyrophosphate synthase (UPPs) structure has been solved using the single wavelength anomalous diffraction method. The putative substrate-binding site is located near the end of the βA-strand with Asp-26 playing a critical catalytic role. In both subunits, an elongated hydrophobic tunnel is found, surrounded by four β-strands (βA-βB-βD- βC) and two helixes (α2 and α3) and lined at the bottom with large residues Ile-62, Leu-137, Val-105, and His-103. The product distributions formed by the use of the I62A, V105A, and H103A mutants are similar to those observed for wild-type UPPs. Catalysis by the L137A UPPs, on the other hand, results in predominantly the formation of the C70 polymer rather than the C55 polymer. Ala-69 and Ala-143 are located near the top of the tunnel. In contrast to the A143V reaction, the C30 intermediate is formed to a greater extent and is longer lived in the process catalyzed by the A69L mutant. These findings suggest that the small side chain of Ala-69 is required for rapid elongation to the C55 product, whereas the large hydrophobic side chain of Leu-137 is required to limit the elongation to the C55 product. The roles of residues located on a flexible loop were investigated. The S71A, N74A, or R77A mutants displayed 25-200-fold decrease in kcat values. W75A showed an 8-fold increase of the FPP Km value, and 22-33-fold increases in the IPP Km values were observed for E81A and S71A. The loop may function to bridge the interaction of IPP with FPP, needed to initiate the condensation reaction and serve as a hinge to control the substrate binding and product release.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

# WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Tuesday, June 20, 2006

| Hide? | Set Name | Query | Hit Count |
|---|---|---|---|
| | | *DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L5 | undecaprenyl pyrophosphate synthase and crystal | 5 |
| ☐ | L4 | undecaprenyl pyrophosphate synthase and crystal | 5 |
| | | *DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L3 | undecaprenyl pyrophosphate synthase and crystal | 4 |
| ☐ | L2 | undecaprenyl pyrophosphate synthase same pneumoniae and crystal | 1 |
| | | *DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ* | |
| ☐ | L1 | undecaprenyl pyrophosphate synthase same pneumoniae and crystal | 2 |

END OF SEARCH HISTORY

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**Search Results** - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: WO 2004087907 A2

L5: Entry 1 of 5 File: EPAB Oct 14, 2004

PUB-NO: WO2004087907A2
DOCUMENT-IDENTIFIER: WO 2004087907 A2
TITLE: CRYSTAL STRUCTURE OF STREPTOCOCCUS UNDECAPRENYL PYROPHOSPHATE SYNTHASE AND USES THEREOF

PUBN-DATE: October 14, 2004

INVENTOR-INFORMATION:

| NAME | COUNTRY |
|---|---|
| FENNELL, KIMBERLY FURLONG | US |
| MANSOUR, MAHMOUD NAIM | US |
| QIU, XIAYANG | US |

INT-CL (IPC): C12 N 9/90
EUR-CL (EPC): C12N009/10

ABSTRACT:

CHG DATE=20041213 STATUS=O>The invention is directed generally to the structure of prenyltransferases, particularly undecaprenyl pyrophosphate synthase, an enzyme important in bacterial cell wall synthesis. The invention relates to the crystal structure of undecaprenyl pyrophosphate synthase from Streptococcus pneumoniae and its interaction with cofactors and ligands. The invention also relates to the structure of ligand and cofactor binding sites of undecaprenyl pyrophosphate synthase.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw. De

☐ 2. Document ID: WO 2004035770 A1

L5: Entry 2 of 5 File: EPAB Apr 29, 2004

PUB-NO: WO2004035770A1
DOCUMENT-IDENTIFIER: WO 2004035770 A1
TITLE: CRYSTAL STRUCTURE OF STAPHYLOCOCCUS UNDECAPRENYL PYROPHOSPHATE SYNTHASE AND USES THEREOF

PUBN-DATE: April 29, 2004

INVENTOR-INFORMATION:

| NAME | COUNTRY |
|---|---|
| PANDIT, JAYVARDHAN | US |
| AMMIRATI, MARK | US |

INT-CL (IPC): C12 N 9/10; C12 N 15/52; G06 F 17/50
EUR-CL (EPC): C12N009/10

ABSTRACT:

CHG DATE=20040511 STATUS=O>The invention is directed generally to the structure of prenyltransferases, particularly undecaprenyl pyrophosphate synthase, an enzyme important in bacterial cell wall synthesis. The invention relates to the crystal structure of undecaprenyl pyrophosphate synthase from Staphylococcus aureus and the interaction with a cofactor and ligands. The invention also relates to the structure of ligand and cofactor binding sites.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

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☐ 3. Document ID: EP 1611234 A2, US 20040191271 A1, WO 2004087907 A2

L5: Entry 3 of 5 File: DWPI Jan 4, 2006

DERWENT-ACC-NO: 2004-698666
DERWENT-WEEK: 200603


TITLE: Streptococcus undecarprenyl pyrophosphate synthase in crystalline form, useful for identifying potential ligand for undecaprenyl pyrophosphate synthase

INVENTOR: FENNELL, K; MANSOUR, M ; QIU, X ; FENNELL, K F ; MANSOUR, M N

PRIORITY-DATA: 2003US-459053P (March 31, 2003), 2004US-0815402 (March 31, 2004)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| EP 1611234 A2 | January 4, 2006 | E | 000 | C12N009/10 |
| US 20040191271 A1 | September 30, 2004 | | 083 | A61K039/02 |
| WO 2004087907 A2 | October 14, 2004 | E | 000 | C12N009/90 |

INT-CL (IPC): A61 K 39/02; C12 N 9/10; C12 N 9/16; C12 N 9/90

ABSTRACTED-PUB-NO: US20040191271A
BASIC-ABSTRACT:

NOVELTY - The Streptococcus undecarprenyl pyrophosphate synthase (I) in crystalline form.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising (I);

(2) a composition (III) comprising Streptococcus undecaprenyl pyrophosphate synthase and a substrate or substrate analog in crystalline form;

(3) identifying (M1) a potential ligand for an undecaprenyl pyrophosphate synthase, by using a three-dimensional structure of the synthase as defined by at least atomic coordinates of amino acid residues 28, 29, 31, 32, 41, 71, 79, 90, 91, and 143, where the atomic coordinates (AC) are of (A) and (B) polypeptide chains of Streptococcus pneumoniae undecaprenyl pyrophosphate synthase, as given in the specification, employing the three-dimensional structure to design or select the potential ligand, obtaining the potential ligand, and contacting the potential ligand with the undecaprenyl pyrophosphate synthase to determine binding of the potential ligand to the synthase;

(4) identifying (M2) a potential inhibitor of a mutant undecaprenyl pyrophosphate synthase, by using a three-dimensional structure of undecaprenyl pyrophosphate synthase by (AC), replacing one or more undecaprenyl pyrophosphate synthase amino acids chosen from 28, 29, 31, 32, 41, 71, 79, 90, 91, 143, 200, 206, 208, 219, and 250 of (S1) in the three-dimensional structure with a different naturally occurring amino acid, thus forming a mutant undecaprenyl pyrophosphate synthase, employing the three-dimensional structure to design or select the potential inhibitor, and contacting the potential inhibitor with the mutant undecaprenyl pyrophosphate synthase or the undecaprenyl pyrophosphate synthase in the presence of a substrate to test the ability of the potential inhibitor to inhibit the undecaprenyl pyrophosphate synthase or the mutant undecaprenyl pyrophosphate synthase;

(5) identifying (M3) a ligand capable of binding to an undecaprenyl pyrophosphate synthase substrate binding site, by introducing into a suitable computer program information defining the binding site comprising first atomic coordinates of amino acids capable of binding to a synthase substrate, where the program displays the three-dimensional structure of the binding site, creating a three-dimensional model of a test compound in the computer program, docking the model of the test compound to the structure of the binding site, creating a second three-dimensional model of the substrate or an inhibitor of the synthase and docking the second model to it, and comparing the docking of the test compound and of the substrate or the inhibitor of the synthase to provide an output of the program;

(6) identifying (M4) a potential inhibitor for an undecaprenyl pyrophosphate synthase, by using a three-dimensional structure of the synthase as defined by (AC), employing the three-dimensional structure to design or select the potential inhibitor, and contacting the potential inhibitor with the synthase in the presence of a substrate to determine the ability of the potential inhibitor to inhibit the synthase;

(7) drug designing (M5) comprising using atomic coordinates of a S. pneumoniae undecaprenyl pyrophosphate synthase having at least one ligand binding site to computationally evaluate relative associations of chemical entities with the ligand binding site and produce an output;

(8) solving (M6) a crystal form comprising using atomic coordinates of a S. pneumoniae undecaprenyl pyrophosphate synthase crystal or its portions, to solve a crystal form of a mutant, homolog or co-complex of the undecaprenyl pyrophosphate synthase by molecular replacement;

(9) a machine readable data storage medium (SM) comprising a data storage material encoded with machine-readable data comprising atomic coordinates comprising amino acid residues 28, 29, 31, 32, 41, 71, 79, 90, 91 and 143 according to (AC);

(10) a computer-implemented tool for design of a drug, comprising a three-dimensional structure of an undecaprenyl pyrophosphate synthase as defined by (AC) of S. pneumoniae undecaprenyl pyrophosphate synthase having at least one ligand

binding site, a model of chemical entity, and a computer program addressing the coordinates and capable of modeling the chemical entity in the ligand binding site to produce an output;

(11) a computer for producing a three-dimensional representation of an undecaprenyl pyrophosphate synthase ligand binding site, comprising a machine readable data storage medium comprising a data storage material encoded with machine-readable data comprising the (AC) comprising the amino acid residues 28, 29, 31, 32, 41, 71, 79, 90, 91, and 143, a working memory for storing instructions for processing the machine readable data, a central processing unit coupled to the working memory and to the machine readable data storage medium for processing the machine readable data into the three-dimensional representation, and a display coupled to the central processing unit for displaying the three-dimensional representation; and (11) preparing (I) comprising incubating the synthase in a hanging drop.

USE - (I) is useful for identifying potential ligand for undecaprenyl pyrophosphate synthase, a ligand capable of binding to undecaprenyl pyrophosphate synthase, and potential inhibitor of mutant undecaprenyl pyrophosphate synthase (claimed).

DESCRIPTION OF DRAWING(S) - The figure shows a crystal structure of Streptococcus pneumoniae undecaprenyl pyrophosphate synthase dimer.



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☐ 4. Document ID: US 20050208639 A1, WO 2004035770 A1, AU 2003269334 A1, EP 1556483 A1

L5: Entry 4 of 5 File: DWPI Sep 22, 2005

DERWENT-ACC-NO: 2004-399868
DERWENT-WEEK: 200563


TITLE: Composition useful for identifying potential ligand of undecaprenyl pyrophosphate synthase, for drug designing or for solving crystal form of mutant synthase, comprises Staphylococcus undecaprenyl pyrophosphate synthase in crystalline form

INVENTOR: AMMIRATI, M; PANDIT, J

PRIORITY-DATA: 2002US-419952P (October 21, 2002), 2003US-0688167 (October 17, 2003)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| US 20050208639 A1 | September 22, 2005 | | 000 | C12N009/12 |
| WO 2004035770 A1 | April 29, 2004 | E | 101 | C12N009/10 |
| AU 2003269334 A1 | May 4, 2004 | | 000 | C12N009/10 |
| EP 1556483 A1 | July 27, 2005 | E | 000 | C12N009/10 |

INT-CL (IPC): C12 N 9/10; C12 N 9/12; C12 N 15/52; G01 N 33/48; G01 N 33/50; G06 F 17/50; G06 F 19/00

ABSTRACTED-PUB-NO: WO2004035770A
BASIC-ABSTRACT:

NOVELTY - A composition (I) comprises Staphylococcus undecaprenyl pyrophosphate synthase in crystalline form, where the synthase has an amino acid sequence at least 80% homologous to a fully defined sequence (S1) of 275 amino acids as given in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a machine-readable data storage medium (II) comprising a data storage material encoded with machine-readable data having atomic coordinates of amino acid residues at positions 33, 34, 36, 37, 46, 76, 84, 95, 96 and 148 of S. aureus undecaprenyl pyrophosphate synthase;

(2) a computer-implemented tool for design of a drug, comprising three-dimensional structure of (I), a model of a chemical entity and a computer program addressing the coordinates and capable of modeling the docking of the chemical entity in a ligand binding site of (I) to produce an output; and

(3) a computer for producing a three-dimensional representation of an undecaprenyl pyrophosphate synthase ligand binding site, comprising a machine-readable data storage medium having a data storage material encoded with machine-readable data with the atomic coordinates of amino acid residues at positions 33, 34, 36, 37, 46, 76, 84, 95, 96 and 148 of S. aureus undecaprenyl pyrophosphate synthase, a working memory for storing instructions for processing the machine-readable data, a central-processing unit coupled to the working memory and to the machine-readable data storage medium for processing the machine readable data into the three-dimensional representation, and a display coupled to the central-processing unit for displaying the three-dimensional representation.

USE - (I) is useful for identifying a potential ligand for undecaprenyl pyrophosphate synthase, which involves using three-dimensional structure of (I) defined by at least atomic coordinates of amino acid residues atomic coordinates of amino acid residues at positions 33, 34, 36, 37, 46, 76, 84, 95, 96 and 148, employing (I) to design or select the potential ligand, obtaining the potential ligand and contacting the potential ligand with (I) to determine binding of the potential ligand to (I). In the above step, the step of obtaining is preceded by the step of employing. (I) is useful for identifying a potential inhibitor of a mutant undecaprenyl pyrophosphate synthase which involves using (I), replacing one or more amino acids of (I) such as amino acids at position 33, 34, 36, 37, 46, 76, 84, 95, 96, 148, 201, 207, 209, 220, and 251 of (S1), with a different naturally occurring amino acid, thus forming mutant synthase, employing the three-dimensional structure to design or select the potential inhibitor, and contacting the potential inhibitor with the mutant synthase, optionally in the presence of a substrate, to test the ability of the potential inhibitor to inhibit the mutant synthase. (I) is useful for identifying a ligand capable of binding to a substrate binding site of (I) which involves introducing into a suitable computer program information defining the binding site, where the information comprises atomic coordinates of amino acids capable of binding to a synthase substrate and a program displays the three-dimensional structure of the binding site, creating a three-dimensional model of a test compound in the computer program, docking the model of the test compound to the binding site of (I), and comparing the docking of the model of the test substance to the docking of known ligands of (I), to provide an output of the program. (I) is useful for identifying a potential inhibitor for (I) which involves using (I), employing (I) to design or select the potential inhibitor and contacting the potential inhibitor with (I) in the presence of a substrate to determine the ability of the potential inhibitor to inhibit (I). (I) is useful for drug designing which involves using (I) having at least one ligand binding site, to computationally evaluate relative associations of chemical entities with the ligand binding site and produce an output. (I) is useful for solving a crystal form which involves using (I) or its portions, to solve a crystal form of a mutant, homolog or co-complex of (I) by molecular replacement (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows a topology of Staphylococcus aureus undecaprenyl pyrophosphate synthase.



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☐ 5. Document ID: AU 2002346643 A8, WO 2003048733 A2, AU 2002346643 A1, EP 1527167 A2

L5: Entry 5 of 5 File: DWPI Nov 10, 2005

DERWENT-ACC-NO: 2003-505322
DERWENT-WEEK: 200634


TITLE: Composition comprising undecaprenyl pyrophosphate synthase, in crystalline form, useful for improving and identifying UPPS inhibitor compounds

INVENTOR: CONCHA, N O; JANSON, C A

PRIORITY-DATA: 2001US-337227P (December 5, 2001)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| AU 2002346643 A8 | November 10, 2005 | | 000 | C12N009/10 |
| WO 2003048733 A2 | June 12, 2003 | E | 516 | G01N000/00 |
| AU 2002346643 A1 | June 17, 2003 | | 000 | G01N000/00 |
| EP 1527167 A2 | May 4, 2005 | E | 000 | C12N009/10 |

INT-CL (IPC): C12 N 9/10; C12 N 9/88; C12 Q 1/00; G01 N 0/00; G06 F 19/00

ABSTRACTED-PUB-NO: WO2003048733A
BASIC-ABSTRACT:

NOVELTY - A composition comprising a undecaprenyl pyrophosphate synthase (UPPS) in crystalline form, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a composition comprising (I) comprising a protein (P) defined by coordinates of native UPPS structure (A1), interatomic distances in an active site of the native UPPS (B1), or interatomic angles in an active site of the native UPPS (C1), in complex with:

(a) the substrate farnesyl pyrophosphate (FPP), and defined by coordinates of active site of UPPS in complex with FPP (A2), interatomic distance is in an active site of UPPS in complex with FPP (B2), or interatomic angles in an active site of UPPS in complex with FPP (C2), as given in the specification; or

(b) the substrate isopentenyl pyrophosphate (IPP), defined by coordinates of active site of UPPS in complex with IPP (A3), interatomic distances in an active site of UPPS in complex with IPP (B3) or interatomic angles in an active site of UPPS in complex with IPP (C3), as given in the specification;

(2) a heavy atom derivative (II) of a Streptococcus pneumoniae UPPS crystal, where

the prenyltransferase comprises a protein having the coordinates of A1-A3, B1-B3, C1-C3;

(3) a composition (III) comprising a co-crystal of S.pneumoniae UPPS in complex with a substrate IPP in orthorhombic crystalline form having a space selected from P212121 and I212121;

(4) a composition (IV) comprising a co-crystal of S.pneumoniae UPPS in complex with a substrate FPP in monoclinic crystalline form having a space group of P21;

(5) determining a crystal structure form using the structural coordinates of a S.pneumoniae UPPS crystal or its portions, to determine a crystal form of a mutant, homolog, or co-complex of a binding pocket or active site by molecular replacement;

(6) identifying an inhibitor compound capable of binding to and inhibiting the enzymatic activity of a S.pneumoniae UPPS the process comprising introducing into a suitable computer program information defining an active site conformation of a UPPS molecule comprising a conformation defined by the coordinates A1, B1 or C1, where the program displays the three-dimensional structure of the coordinates, creating a three dimensional structure of a test compound in the computer program, displaying and superimposing a model of the test compound on a model of the active site, incorporating the test compound in a biological prenyltransferase activity assay for a prenyltransferase characterized by the active site, and determining whether the test compound inhibits enzymatic activity in the assay;

(7) designing drugs useful for inhibiting UPPS activity using the atomic coordinates of a S.pneumoniae UPPS crystal to computationally evaluate a chemical entity for associating with a active site of a UPPS enzyme;

(8) modifying (M1) a test UPPS polypeptide by providing a test UPPS polypeptide sequence having a characteristic that is targeted for modifications, aligning the test UPPS polypeptide sequence with at least one reference UPPS polypeptide sequence for which an X-ray structure is available, where the at least one reference UPPS polypeptide sequence has a characteristic that is desired for the test UPPS polypeptide, building a three-dimensional model for the test UPPS polypeptide using the three-dimensional coordinates of the X-ray structure(s) of the at least one reference UPPS polypeptide and its sequence alignment with the test UPPS polypeptide sequence, examining the three-dimensional model of the test UPPS polypeptide for a difference in an amino acid residue as compared to the at least one reference polypeptide, where the residues are associated with the desired characteristic, and mutating an amino acid residue in the test UPPS polypeptide sequence located at a difference identified in above step, to a residue associated with the desired characteristic, whereby the test UPPS polypeptide is modified;

(9) identifying (M2) an inhibitor compound capable of inhibiting the enzymatic activity of a Streptococcus pneumoniae UPPS comprising coordinates defined by A1, B1, C1, involves carrying out an in vitro assay by introducing the compound in a biological prenyltransferase activity assay containing the prenyltransferase, and determining whether the test compound inhibits the enzymatic activity of the prenyltransferase in the assay;

(10) a product of (M1) or (M2), which is a peptide, peptidomimetic, or synthetic molecule and is useful for inhibiting a metallo-beta lactamase in treatment of bacterial infectious in a mammal; and

(11) designing drugs (M3) useful for inhibiting S.pneumoniae UPPS comprising using the atomic coordinates of a S.pneumoniae UPPS crystal or the atomic coordinates of a S.pneumoniae in complex with FPP or IPP to computationally evaluate a chemical entity for associating with the active site of a S.pneumoniae UPPS.

ACTIVITY - Antibacterial.

MECHANISM OF ACTION - Metallo- beta -lactamase inhibitor.

No suitable data given.

USE - The product is useful for inhibiting a metallo- beta -lactamase in treatment of bacterial infections in a mammal (claimed). The crystalline structure of UPPS is useful for improving and identifying UPPS inhibitor compounds.





| Terms | Documents |
|---|---|
| undecaprenyl pyrophosphate synthase and crystal | 5 |

# Hit List

First Hit | Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

**Search Results** - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 20050208639 A1

L3: Entry 1 of 4 File: PGPB Sep 22, 2005

PGPUB-DOCUMENT-NUMBER: 20050208639
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050208639 A1

TITLE: Crystal structure of staphylococcus undecaprenyl pyrophosphate synthase and uses thereof

PUBLICATION-DATE: September 22, 2005

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY |
|---|---|---|---|
| Ammirati, Mark | Stonington | CT | US |
| Pandit, Jayvardhan | Mystic | CT | US |

US-CL-CURRENT: 435/194; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20050038611 A1

L3: Entry 2 of 4 File: PGPB Feb 17, 2005

PGPUB-DOCUMENT-NUMBER: 20050038611
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050038611 A1

TITLE: S8 rrna-binding protein from the small ribosomal subunit of staphylococcus aureus

PUBLICATION-DATE: February 17, 2005

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY |
|---|---|---|---|
| Concha, Nestor O. | King of Prussia | PA | US |
| Gontarek, Richard K | King of Prussia | PA | US |
| Janson, Cheryl A | Hinsdale | IL | US |

US-CL-CURRENT: 702/20; 435/6, 530/358

☐ 3. Document ID: US 20040219653 A1

L3: Entry 3 of 4 File: PGPB Nov 4, 2004

PGPUB-DOCUMENT-NUMBER: 20040219653
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040219653 A1

TITLE: Crystal structure of homo sapiens adipocyte lipid binbing protein and uses thereof

PUBLICATION-DATE: November 4, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY |
|---|---|---|---|
| Qiu, Xiayang | Mystic | CT | US |

US-CL-CURRENT: 435/198; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 4. Document ID: US 20040191271 A1

L3: Entry 4 of 4 File: PGPB Sep 30, 2004

PGPUB-DOCUMENT-NUMBER: 20040191271
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040191271 A1

TITLE: Crystal structures of streptococcus undecaprenyl pyrophosphate synthase and uses thereof

PUBLICATION-DATE: September 30, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | COUNTRY |
|---|---|---|---|
| Fennell, Kimberly F. | Niantic | CT | US |
| Mansour, Mahmoud N. | Groton | CT | US |
| Qiu, Xiayang | Mystic | CT | US |

US-CL-CURRENT: 424/190.1; 435/196

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

| Terms | Documents |
| --- | --- |
| undecaprenyl pyrophosphate synthase and crystal | 4 |

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